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| 09/744,315      | 06/25/2001  | Y. Tom Tang          | PF-0567 USN         | 5059             |

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EXAMINER

DIBRINO, MARIANNE NMN

ART UNIT PAPER NUMBER

1644

DATE MAILED: 03/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/744,315

Applicant(s)

TANG ET AL.

Examiner

DiBrino Marianne

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 21-40 is/are pending in the application.
- 4a) Of the above claim(s) 21 and 29-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 22-28 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 10/20/03
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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### DETAILED ACTION

1. Applicant's amendment filed 10/29/03 is acknowledged and has been entered.
2. Applicant's election with traverse of Group VII (corresponding to newly added claims 22-28 in Applicant's amendment filed 10/29/03 is acknowledged.

The basis for the traversal is of record in the said amendment.

Applicant's arguments have been fully considered but are not persuasive.

It is the Examiner's position that MPEP 1893.03(d) provides that "applicant would have a right to include in a single application only those inventions which are so linked as to form a single general inventive concept. A group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature. The expression special technical features is defined [in PCT Rule 13.2] as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art." MPEP 1893.03(d) also provides "If the examiner finds that a national stage application lacks unity of invention under 1.475, the examiner may in an Office Action require the applicant in the response to that action to elect the invention to which the claims shall be restricted." It is the Examiner's further position that the reference Zhao et al taught the recited invention at the time lack of unity was made in the prior office action mailed 9/26/03.

Regarding Applicants comments about undue burden, the M.P.E.P. 803 (July 1998) states that: For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search.

The instant invention (i.e., instant claims 22-28) is classified in Class 536, subclass 23.1.

- a. claim 33 is drawn to a method of screening for a compound that binds to a polypeptide and is classified in Class 435, subclass 7.1
- b. claim 34 is drawn to a method of screening for a compound that alters expression of a polynucleotide, classified in Class 435, subclass 6
- c. claims 29, 35 and 37 are drawn to a method of detecting a polynucleotide in a sample or assessing the toxicity of a test compound or of generating an expression profile, respectively, comprising hybridization with a probe, classified in Class 435, subclass 6
- d. claim 30 is drawn to a method of detecting a target polynucleotide in a sample comprising PCR amplification, classified in Class 435, subclass 91.2
- e. claim 36 is drawn to a microarray, classified in Class 536, subclass 24.3
- f. claims 38-40 are drawn to an antibody/fragment thereof and composition thereof, classified in Class 530, subclass 387.1 and Class 424, subclass 130.1

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g. claims 21, 31 and 32 are drawn to a polypeptide/fragment thereof and composition thereof, classified in Class 530, subclass 350

The separate classification and different field of search therefore establishes that serious burden is placed on the Examiner by the examination of additional Groups

Accordingly, claims 21 and 29-40 (newly added claims 21, 31 and 32 corresponding to non-elected Groups I-VI, newly added claims 38-40 corresponding to non-elected Groups XIII-XVIII, newly added claims 33-37 discussed supra) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 22-28 are currently being examined.

3. The amendment filed 10/29/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference of the provisional application serial nos. 60/155,203 and 60/155,524 made after the time of filing.

4. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 22-28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Claims 22-28 are drawn to polynucleotides encoding a polypeptide comprising an amino acid sequence of SEQ ID NO: 1 (including SEQ ID NO: 7, variants or complements or RNA equivalents thereof, including a naturally occurring polynucleotide sequence with at least 90% sequence identity to a polynucleotide sequence of SEQ ID NO: 7), or at least 90% identical to SEQ ID NO: 1 or an immunogenic fragment of a polypeptide consisting of an amino acid fragment of SEQ ID NO: 1, wherein said fragment comprises at least 20 contiguous amino acid residues of SEQ ID NO: 1 or at least 60 contiguous nucleotides of the polynucleotide recited in instant claim 27, further comprising a promotor operably linked thereto, and host cell comprising said polynucleotide and method of producing the said polypeptide comprising culturing the said cell.

The specification discloses the isolation of several polynucleotide clones encoding proteins having significant sequence similarity to known human epidermal proteins. The specification discloses that HEPI-1 through HEPI-6 are human epidermal proteins (page 14 at lines 25-26). The specification further discloses that chemical and structural similarity in the context of

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sequences and motifs, exists between regions of HEPI and human epidermal proteins and that expression of HEPI is closely associated with cell proliferation, cancer, inflammation and immune response. Based on the structural similarity, the specification asserts that the newly disclosed sequences encoding HEPI have the utility of having similar activities. The specification discloses "Therefore, HEPI appears to play a role in epithelial, cell proliferative and autoimmune/inflammatory disorders." The specification discloses a list of disorders that can be treated or prevented by administration of HEPI (page 25 at lines 23-35 and page 26 at lines 1-29).

However, Tables 1 and 3 of the specification disclose that SEQ ID NO: 7 is expressed not only in dermatologic tissue, but also in reproductive tissue and hematopoietic tissue, and is found by hybridization studies to be present in some cases of proliferation, cancer or inflammation. Therefore, the data disclosed in the specification indicate widespread expression.

In addition, the assertion that the disclosed HEPI sequences encode polypeptides that have biological activities similar to the database polypeptides cannot be accepted in the absence of supporting evidence, because the relevant literature reports numerous examples of structurally related polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF family displaying a high degree of global homology with naturally occurring PDGF) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen in vivo, wherein endothelial pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125: 1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al (Proc. Natl. Acad. Sci. USA, Vol. 93, 1996, pages 9021-9026) disclose that OP-1, a member of the TGF- $\beta$  family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- $\beta$  family members BMP-2 and TGF- $\beta$  1 had no effect on metanephrogenesis under identical conditions (especially page 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-b family (1987, Cell 49: 437-8, especially p. 438, column 1, second full paragraph to the end). OP-1, BMP-2 and TGF- $\beta$  1 all display a high degree of global homology with one another. Similarly, PTH and PTHrP are two structurally related proteins which can have opposite effects on bone resorption (Pillbeam et al, Bone, Vol. 14, 1993, pages 717-720, especially page 717, second paragraph of Introduction). Finally, Kopchick et al (U.S. Patent No. 5, 350, 836) discloses several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid residue (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based on structural similarity to a protein found in the sequence databases. For example, Skolnick et al (2000, Trends in Biotech. 18: 34-39) state that knowing the protein structure by itself is insufficient to annotate a

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number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, *Genome Research* 10: 398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are echoed by Doerks et al (1998, *Trends in Genetics* 14: 248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al (1997, *Nature Biotechnology* 15: 1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, *Trends in Genetics* 15: 132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al (1996, *Trends in Genetics* 12: 425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al (*Science*, Vol. 247, 1990, pages 1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (especially page 1306). Thus, the specification fails to establish the asserted credible, specific and substantial utility of HEPI activity.

The specification does not support a credible, specific and substantial utility regarding the claimed polynucleotides encoding HEPI and variants/fragments thereof for purposes unrelated to the asserted biological activity. In addition, the specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotide, i.e., that the claimed HEPI are expressed, overexpressed, underexpressed or aberrantly expressed in the disorders listed in a specific, diseased tissue compared to the healthy tissue control, and that said polypeptides are clinically related to said disorders.

In addition, the specification contains assertions that the claimed polynucleotides can be used in gene monitoring assays, which are used in the art for drug development and toxicology studies (page 38). However, without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean. For example, if a compound is tested on a microarray comprising the claimed polynucleotides and affects expression of the polynucleotides negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would exacerbate the disease if administered. The test results also would not have meaning in terms of what specific disease is relevant. The asserted utility in gene expression monitoring assays is thus not substantial, because significant further

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research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue. Furthermore, since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides. Lu et al (2003 Preclinica 31-42) teaches "For discovery of therapeutics to control disease, a need to go beyond identification of disease-causing genes and proteins has begun to be recognized (30). The biological incentive and desired outcome of drug intervention is just that, the intervention in the disease process or pathology. Thus, improvement of data sets to include information on causation of disease, unfortunately, still does not address the key to identify and select drug targets, namely biologic control functions. The evidence is growing that the identification of disease-causing genes has not proven to facilitate identification of viable small molecule drug targets. One clear example, reviewed recently (30), can be found in the hereditary breast cancer genes *Brcal* and *Brca2*, which may be excellent for diagnostics, but so far have failed for therapeutics. Unfortunately, the problem is exacerbated by low predictability of in vitro cell models and model organisms for gene and protein roles even in animal disease models and even lower predictability for human disease." (see paragraph spanning pages 35-36).

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polynucleotides. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 22-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. Specifically, since the claimed invention in claims 22-28 is not supported by either a credible, specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

b. Furthermore, the specification does not disclose how to make a polynucleotide encoding a polypeptide: a naturally occurring amino acid sequence at least 90% polynucleotide sequence identity to SEQ ID NOS: 1, an immunogenic fragment of an amino acid of SEQ ID NO: 1,

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a complementary sequence to SEQ ID NO: 7 or a naturally occurring polynucleotide with at least 90% sequence identity to SEQ ID NO: 7 or complementary sequence thereof, or an RNA equivalent thereof and including the isolated polynucleotide comprising at least 60 contiguous nucleotides of the polypeptide recited in instant claim 27. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass polynucleotides which encompass sequences that are not HEPI SEQ ID NOS: 7, or polynucleotides encoding polypeptides that are not SEQ ID NOS: 1, respectively, and do not retain activity.

The instant specification discloses that SEQ ID NO: 1 is HEPI polypeptide 1. With regard to naturally-occurring polynucleotide sequence with at least 90% sequence identity to a polynucleotide sequence of SEQ ID NO: 7, or an isolated polynucleotide encoding...a naturally occurring amino acid sequence with at least 90% sequence identity to a polypeptide of SEQ ID NO: 1, the specification on page 14 at lines 3-23 discloses that a "variant" of HEPI polypeptides refers to an amino acid sequence that is altered by one or more amino acid residue, and may include deletions, insertions or both, and may include conservative as well as non-conservative substitutions. The specification further discloses that a polynucleotide "variant" may encompass a polynucleotide related to HEPI and may include allelic, splice, species or polymorphic variants. The specification on page 9 at lines 7-11 discloses that biological or immunological activity refers to a protein having structural, regulatory or biochemical functions of a naturally occurring molecule, or the capability to induce a specific immune response and to bind with specific antibodies, respectively.

There is no guidance in the specification as to what alterations result in a functional variant/fragment/naturally occurring sequence with at least 90% sequence identity other than the disclosure on page 14 at lines 3-23 that guidance for which amino acid residues may be substituted, inserted or deleted without abolishing biological or immunological activity may be found using a software program, LASERGENE. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain functional activity, especially as evidenced by the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are therefore not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, Merz & LeGrand, Birkhauser Boston, pages 491-495, 1994, entire article, especially Section 6, paragraph 1), it would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make the corresponding sequences, and it would therefore require undue experimentation to make the corresponding polynucleotide sequences. In addition the specification fails to provide guidance regarding what deletions from or alterations in the disclosed sequence result in polynucleotides that encode variants of SEQ ID NOS: 7 or polynucleotides encoding SEQ ID NOS: 1. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of polynucleotide variants where the expectation of retaining similar



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encoding function is unpredictable based on the instant disclosure. Detailed information regarding the structural and functional requirements of HEPI proteins is lacking. Therefore, predicting which amino acid variants would maintain function is well outside the realm of routine experimentation; thus a skilled artisan would require guidance, such as information regarding the location, size and sequence of deletions and alterations which preserve the encoding activity, in order to make and use polynucleotides, vectors, host cells and recombinant methods of the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

8. Claims 22-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed polynucleotide encoding a biologically active fragment of a polypeptide of SEQ ID NO: 1, nor the naturally occurring polynucleotide sequence with at least 90% identity to SEQ ID NO: 7, nor the polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence with at least 90% sequence identity to SEQ ID NO: 1, and complements and RNA equivalents thereof, and expression vector and host cell comprising said polynucleotide. There is insufficient disclosure in the specification for the aforementioned polynucleotide and expression vector and host cell comprising said polynucleotide.

The instant specification discloses that SEQ ID NO: 1 is HEPI polypeptide 1. With regard to naturally-occurring polynucleotide sequence with at least 90% sequence identity to a polynucleotide sequence of SEQ ID NO: 7, or an isolated polynucleotide encoding...a naturally occurring amino acid sequence with at least 90% sequence identity to a polypeptide of SEQ ID NO: 1, the specification on page 14 at lines 3-23 discloses that a "variant" of HEPI polypeptides refers to an amino acid sequence that is altered by one or more amino acid residue, and may include deletions, insertions or both, and may include conservative as well as non-conservative substitutions. The specification further discloses that a polynucleotide "variant" may encompass a polynucleotide related to HEPI and may include allelic, splice, species or polymorphic variants. The specification on page 9 at lines 7-11 discloses that biological or immunological activity refers to a protein having structural, regulatory or biochemical functions of a naturally occurring molecule, or the capability to induce a specific immune response and to bind with specific antibodies, respectively.

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The instant specification does not disclose what sequence is necessary for biological activity, nor what the biological activity is. The specification does not disclose the claimed polynucleotide with the limitations delineated supra. Thus, at the time the application was filed, the claimed polynucleotide was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention.

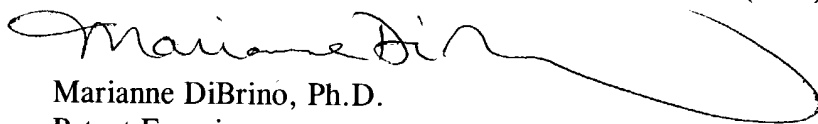
9. No claim is allowed.

10. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.


11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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